OsteoArthritis and Cartilage (2007) **15,** 789–797

doi:10.1016/j.joca.2007.01.011

Osteoarthritis and Cartilage

International Cartilage Repair Society

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

In vivo $T_{1\rho}$ and T_2 mapping of articular cartilage in osteoarthritis of the knee using 3 T MRI

X. Li Ph.D.†*, C. Benjamin Ma M.D.‡, T. M. Link M.D.†, D.-D. Castillo B.S.†, G. Blumenkrantz B.S.†, J. Lozano B.S.†‡, J. Carballido-Gamio Ph.D.†, M. Ries M.D.‡ and S. Majumdar Ph.D.†

† *Musculo-skeletal Quantitative Imaging Research (MQIR), Department of Radiology, University of California at San Francisco (UCSF), San Francisco, CA, USA*

‡ *Department of Orthopaedic Surgery, UCSF, San Francisco, CA, USA*

Summary

Objective: Evaluation and treatment of patients with early stages of osteoarthritis (OA) is dependent upon an accurate assessment of the cartilage lesions. However, standard cartilage dedicated magnetic resonance (MR) techniques are inconclusive in quantifying early degenerative changes. The objective of this study was to determine the ability of MR T1rho ($T_{1\rho}$) and T_2 mapping to detect cartilage matrix degeneration between normal and early OA patients.

Method: Sixteen healthy volunteers (mean age 41.3) without clinical or radiological evidence of OA and 10 patients (mean age 55.9) with OA were scanned using a 3 Tesla (3 T) MR scanner. Cartilage volume and thickness, and $T_{1\rho}$ and T_2 values were compared between normal and OA patients. The relationship between $T_{1\rho}$ and T_2 values, and Kellgren–Lawrence scores based on plain radiographs and the cartilage lesion grading based on MR images were studied.

Results: The average $T_{1\rho}$ and T_2 values were significantly increased in OA patients compared with controls (52.04 ± 2.97 ms vs 45.53 ± 3.28 ms with $P = 0.0002$ for $T_{1\rho}$, and 39.63 ± 2.69 ms vs 34.74 ± 2.48 ms with $P = 0.001$ for T_2). Increased $T_{1\rho}$ and T_2 values were correlated with increased severity in radiographic and MR grading of OA. $T_{1\rho}$ has a larger range and higher effect size than T_2, 3.7 vs 3.0.

Conclusion: Our results suggest that both *in vivo* $T_{1\rho}$ and T_2 relaxation times increase with the degree of cartilage degeneration. $T_{1\rho}$ relaxation time may be a more sensitive indicator for early cartilage degeneration than T_2. The ability to detect early cartilage degeneration prior to morphologic changes may allow us to critically monitor the course of OA and injury progression, and to evaluate the success of treatment to patients with early stages of OA.

Key words: Osteoarthritis, Cartilage imaging, Magnetic resonance imaging, $T_{1\rho}$, T_2.

Introduction

Osteoarthritis (OA) is a heterogeneous and multifactorial disease characterized primarily by the progressive loss of hyaline articular cartilage[1]. Plain radiographs have been used primarily in the evaluation of OA, which depict only narrowing of the joint space or gross osseous changes that tend to occur late in the disease. Early changes in the articular cartilage may not be visible on plain radiographs. Cartilage loss can only be indirectly inferred by the development of joint space narrowing, which can be highly unreliable even with careful attention to proper technique[2]. In addition, plain radiographs are insensitive to focal cartilage loss, and widening of the joint space despite significant cartilage loss can occur in one compartment of the knee simply as a result of narrowing in the other compartment[3].

Magnetic resonance imaging (MRI) has been found useful to visualize cartilage directly yet morphologic imaging shows damage at a stage when cartilage is already irreversibly lost. Standard cartilage dedicated magnetic resonance (MR) techniques include fat-saturated T_2-weighted, proton density-weighted fast spin echo (FSE) sequences and T_1-weighted spoiled gradient echo (SPGR) sequences. These sequences, however, are inconclusive in quantifying early degenerative changes of the cartilage matrix, especially biochemical changes such as proteoglycan (PG) loss[4]. Early events in the development of cartilage matrix breakdown include the loss of PGs, changes in water content, and molecular level changes in collagen[5]. Early diagnosis of cartilage injury would require the ability to noninvasively detect changes in PG concentration and collagen integrity before gross morphologic changes occur.

T_2 relaxation reflects the ability of free water proton molecules to move and to exchange energy inside the cartilaginous matrix. Damage to collagen—PG matrix and increase of water content in degenerating cartilage may increase T_2 relaxation times. *In vivo* T_2 relaxation times have been derived by several groups[6–10]. Elevated T_2 values were observed in patients with OA[7,10]. T1rho ($T_{1\rho}$) relaxation time has recently been proposed as an attractive alternative parameter to probe biochemical changes in cartilage[11–15]. The $T_{1\rho}$ parameter describes the spin–lattice relaxation in the rotating frame[16]. It probes the slow motion interactions between motion-restricted water molecules and their local

*Address correspondence and reprint requests to: Dr Xiaojuan Li, Ph.D., Department of Radiology, University of California at San Francisco, 185 Berry Street, Suite 350, San Francisco, CA 94107, USA. Tel: 1-415-353-4909; Fax: 1-415-353-3438; E-mail: xiaojuan.li@radiology.ucsf.edu

Received 20 October 2006; revision accepted 6 January 2007.

macromolecular environment. The extracellular matrix in the articular cartilage provides a motion-restricted environment to water molecules. Changes to the extracellular matrix, such as PG loss, therefore may be reflected in measurements of $T_{1\rho}$. Initial studies in human subjects showed elevated $T_{1\rho}$ values in patients with OA[17–19]. Although both $T_{1\rho}$ and T_2 can probe slow motion of water protons, they are parameters describing different MR relaxation mechanisms. $T_{1\rho}$ is spin–lattice relaxation related with the energy changes between proton spins and the environment, while T_2 is spin–spin relaxation related with the energy changes between proton spins themselves. Therefore, these two parameters may provide complementary information regarding macromolecular changes in cartilage.

With the improvement in cartilage resurfacing procedures and development of disease modifying drugs for OA, there is a need to develop a noninvasive method to monitor early cartilage degeneration or restoration[20–23]. In this study, we investigated the changes in $T_{1\rho}$ and T_2 relaxation times in normal and osteoarthritic patients using 3 T MRI. Our hypothesis was that there would be an increase in both $T_{1\rho}$ and T_2 values in cartilage in osteoarthritic patients compared to normal controls. We further hypothesized that the amount of $T_{1\rho}$ and T_2 elevation would be related to the severity of OA.

Materials and methods

SUBJECTS

Sixteen healthy volunteers (eight females and eight males, ranging in age from 22 to 74 years, with an average age of 41.3 years) and 10 patients with clinical OA symptoms and radiological findings (three females and seven males, ranging in age from 37 to 72 years, with an average age of 55.9 years) were studied. Among them 10 healthy volunteers (four females and six males, ranging in age from 28 to 74 years, with an average age of 41.0 years) were scanned for both $T_{1\rho}$ and T_2 mapping, while in the remaining six volunteers only $T_{1\rho}$ mapping was obtained. In all the patients standard radiographs were obtained in addition to both $T_{1\rho}$ and T_2 MR examinations. The study was approved by the Committee for Human Research at our institution and all the subjects gave informed consent.

IMAGING PROTOCOL

In the patients, the standard knee radiographic protocol included (1) bilateral standing flexion weight-bearing view, (2) 30° flexion lateral, and (3) bilateral patellofemoral, sunrise views.

All MR exams were implemented on a 3 T GE Excite Signa MR scanner using a quadrature transmit/receive knee coil. The protocol included six sequences: sagittal T_1-weighted spin echo (SE) imaging (time of repetition (TR)/time of echo (TE) = 700/13.5 ms, field of view (FOV) = 16 cm, matrix = 288 × 224, bandwidth = 15.63 kHz, number of excitations [NEX] = 2), sagittal and axial three-dimensional (3D) water excitation high-resolution SPGR imaging (TR/TE = 15/6.7 ms, flip angle = 12°, FOV = 16 cm, matrix = 512 × 512, slice thickness = 1 mm, bandwidth = 31.25 kHz, NEX = 0.75), sagittal fat-saturated T_2-weighted FSE images (TR/TE = 3700/68 ms, FOV = 14 cm, matrix = 288 × 224, slice thickness = 3 mm, echo train length [ETL] = 8, bandwidth = 16.5 kHz, NEX = 2), and axial $T_{1\rho}$-weighted and T_2-weighted images.

The multi-slice $T_{1\rho}$-weighted images were obtained using the sequence we previously developed based on spin-lock techniques and spiral image acquisition[19]. The acquisition parameters were as follows: 14 interleaves/slice, 4096 points/interleaf, FOV = 16 cm, effective in-plane spatial resolution = 0.6 × 0.6 mm, slice thickness = 3 mm, skip = 1 mm, number of slices = 14–16, TR/TE = 2000/5.8 ms, time of spin-lock (TSL) = 20/40/60/80 ms, and spin-lock frequency = 500 Hz. The total acquisition time was approximately 13 min. The axial $T_{1\rho}$-weighted images were prescribed on sagittal SPGR images, covering regions from the top of the patellar cartilage to the femoral–tibial cartilage. The T_2 quantification sequence was also based on spiral sequence[24,25] with TR/TE = 2000/6.7, 12, 28, 60 ms. All other prescription parameters of the T_2 sequence were the same as the $T_{1\rho}$ sequence, with a total acquisition time of approximately 11 min. The T_2 quantification was acquired subsequently and covered the same region as the $T_{1\rho}$ sequence.

PLAIN RADIOGRAPHIC AND CLINICAL DIAGNOSTIC MR IMAGES' ASSESSMENT

All radiographs and clinical MR images (SPGR, T_1- and T_2-weighted fat-saturated sequences) were reviewed by a radiologist (TML). The radiographic findings were scored according to the Kellgren–Lawrence (KL) scale, which is a standard grading system for OA[26,27]. Osteophytes at the joint margins, narrowing of the joint spaces and subchondral sclerosis have been considered as radiological features of OA. Based on these features, the following KL scores were defined[28]: 0, no features of OA; 1, doubtful OA, with minute osteophytes of doubtful importance; 2, minimal OA, with definite osteophytes but unimpaired joint space; 3, moderate OA, with osteophytes and moderate diminution of joint space; and 4, severe OA, with greatly impaired joint space and sclerosis of subchondral bone.

The MR images were analyzed regarding cartilage lesions, joint effusion, popliteal cysts, ligaments and menisci. Additional features included reactive bone marrow changes, osteophytes, subchondral cysts and loose bodies. Five compartments were defined in each subject: patella (P), medial femoral condyle (MFC), lateral femoral condyle (LFC), medial tibia (MT) and lateral tibia (LT). Cartilage thinning was defined in each of the compartments based on T_2-weighted FSE and T_1-weighted SPGR images as follows: 0, no obvious thinning; 1, <50% thinning; 2, >50% thinning; and 3, full thickness loss of cartilage. Each patient was given an overall grade based on the most severe cartilage lesion in each of the five compartments. The bone marrow edema (BME) pattern was defined as high signal intensity in the T_2-weighted fat-saturated FSE images and graded as follows: 0, no obvious BME; 1, mild edema with less than 1 cm diameter in the long axis; 2, moderate edema with diameter between 1 and 3 cm in the long axis; and 3, severe edema with diameter larger than 3 cm in the long axis. Osteophytes were classified as follows: 0, no obvious osteophytes; 1, mild when they were located in the joint margins and were less than 0.5 cm in diameter; and 2, severe when osteophytes were larger than 0.5 cm in diameter.

MR IMAGES POST-PROCESSING

MR images were transferred to a Sun workstation (Sun Microsystems, Palo Alto, CA) for off-line quantification of cartilage volume and thickness, and for quantification of $T_{1\rho}$ and T_2 relaxation times.

Cartilage was segmented semiautomatically in sagittal SPGR images using an in-house developed program with MATLAB based on edge detection and Bezier splines[29].

Five compartments were defined as mentioned above in each subject: P, MFC, LFC, MT and LT. An iterative minimization process was used to calculate total cartilage volume and average thickness for each region. Following segmentation, a medial line was generated in each region of the cartilage. The cartilage thickness was determined by calculating the minimum distance from each point on the medial line to a cartilage boundary. The average thickness was calculated for each slice and then averaged for all the slices. The cartilage volume was determined by multiplying the total number of voxels encompassing the cartilage by the volume of each voxel. The root mean square coefficient of variation for intra-observer reproducibility of this algorithm was between 2.4% and 3.69% as reported previously[30]. Finally to minimize volumetric variations due to the size of the knee, the cartilage volume was normalized by the epicondylar distance determined from axial SPGR images.

The $T_{1\rho}$ map was reconstructed by fitting the image intensity pixel-by-pixel to the equation below using a Levenberg–Marquardt mono-exponential fitting algorithm developed in-house:

$$S(\mathrm{TSL}) \propto \exp(-\mathrm{TSL}/T_{1\rho})$$

$T_{1\rho}$-weighted images with the shortest TSL (therefore with highest signal to noise ratio) were rigidly registered to high-resolution T_1-weighted SPGR images acquired in the same exam using the VTK CISG Registration Toolkit[31]. The transformation matrix was applied to the reconstructed $T_{1\rho}$ map. Different regions of the knee cartilage—patellar, trochlea, medial and lateral compartments—were segmented automatically based on axial high-resolution SPGR images using the same algorithm used for sagittal segmentation. The segmentation was corrected manually to avoid synovial fluid or other surrounding tissue. 3D cartilage contours were generated and overlaid on the registered $T_{1\rho}$ map. Similarly, The T_2 map was reconstructed by fitting the image intensity pixel-by-pixel to the equation $S(\mathrm{TE}) \propto \exp(-\mathrm{TE}/T_2)$. T_2-weighted images with the shortest TE were rigidly registered to the SPGR images, and the transformation matrix was applied to T_2 maps using the VTK CISG Registration Toolkit. The cartilage contours generated previously from the SPGR images were also overlaid on the registered T_2 map. To reduce artifacts caused by partial volume effects with synovial fluid, regions with relaxation time greater than 150 ms in $T_{1\rho}$ or T_2 maps were manually removed from the data used for quantification.

STATISTICAL ANALYSIS

A nonparametric rank test was used to compare volume, average thickness, average $T_{1\rho}$ and T_2 values between control subjects and OA patients. A Spearman rank correlation was performed to study the relationship between average $T_{1\rho}$ and T_2 values, between these relaxation times and ages, and between these relaxation times and cartilage thickness and volumes. The effect size was calculated to compare the discrimination power of $T_{1\rho}$ and T_2 values using the equation below:

$$\text{Effect size} = \Delta\text{mean}/\text{SD}$$

where Δmean is the mean difference between control and OA, and SD is the pooled standard deviation of these two groups defined as

$$\text{SD} = \sqrt{(n_1-1)\text{SD}_1^2 + (n_2-1)\text{SD}_2^2/(n_1+n_2-2)}$$

where n_1 and n_2 are the sample sizes of these two groups, respectively, and SD_1 and SD_2 are the standard deviations of these two groups, respectively.

Results

$T_{1\rho}$ AND T_2 QUANTIFICATION FOR CONTROL SUBJECTS AND OA PATIENTS

The average $T_{1\rho}$ values were significantly higher in OA subjects compared with healthy controls (52.04 ± 2.97 ms vs 45.53 ± 3.28 ms, $P = 0.0002$), as shown in Table I. The average T_2 values were also increased significantly in patients with OA (39.63 ± 2.69 ms vs 34.74 ± 2.48 ms, $P = 0.001$, Table I). Figure 1 shows $T_{1\rho}$ and T_2 maps for a healthy control. Figures 2 and 3 present $T_{1\rho}$ and T_2 maps of a patient with mild OA with KL score = 1, and a patient with advanced OA with KL score = 4, respectively. The average $T_{1\rho}$ and T_2 values correlated significantly ($R^2 = 86.0\%$, $P < 0.0001$). $T_{1\rho}$ values had a higher effect size than T_2 values (3.7 vs 3.0), indicating $T_{1\rho}$ may be more sensitive than T_2 for distinguishing OA from controls.

The average $T_{1\rho}$ values increased with age in the 16 healthy controls, with a significant but moderate correlation ($R^2 = 58.3\%$, $P = 0.018$), as shown in Fig. 4. In the 10 controls who also had T_2 quantification, T_2 values also increased with ages, but the correlation was not significant ($R^2 = 41.5\%$, $P = 0.233$).

KL SCORES AND MR FINDINGS BASED ON ANATOMIC MR IMAGES

Based on radiographs, two patients had a KL score = 1, three had a KL score = 2, three had a KL score = 3 and two had a KL score = 4. Cartilage lesions were classified as grade 0 for one patient, 1 for three patients, 2 for two patients and 3 for four patients. Tables II(a) and (b) illustrate the main findings based on radiographs and clinical MR images for the 10 patients, including KL score, cartilage lesion grade in each compartment, osteophytes in the femorotibial joint, femoro-patellar joint and the joint center, as well as BME. Among the 10 OA patients, six patients had more severe cartilage lesions at the medial compartments than at the lateral compartments, two had more severe

Table I
Radiological findings based on radiographs and anatomic MR images

Patient ID	KL score	Cartilage thinning					Osteophytes			BME
		MFC	LFC	MT	LT	P	F–T	F–P	Center	
1	2	1	0	0	0	2	1	1	0	0
2	1	1	1	0	0	0	1	1	0	0
3	2	0	1	0	1	1	1	1	1	2
4	3	2	0	2	0	2	2	2	1	2
5	3	3	0	3	0	2	1	1	0	2
6	1	1	0	0	0	1	1	1	0	3
7	4	3	2	3	2	3	2	1	1	2
8	3	2	3	2	2	3	1	1	0	2
9	2	0	0	0	0	0	0	1	0	0
10	4	3	0	3	0	1	3	2	0	2

F–T: femoral–tibial joint; F–P: femoral–patellar joint. Cartilage thinning grading: 1, <50% thinning; 2, >50% thinning; and 3, full thinning (loss) of cartilage. BME grading: 0, no obvious BME; 1, mild edema with less than 1 cm diameter in the long axis; 2, moderate edema with diameter between 1 and 3 cm in the long axis; 3, severe edema with diameter larger than 3 cm in the long axis.

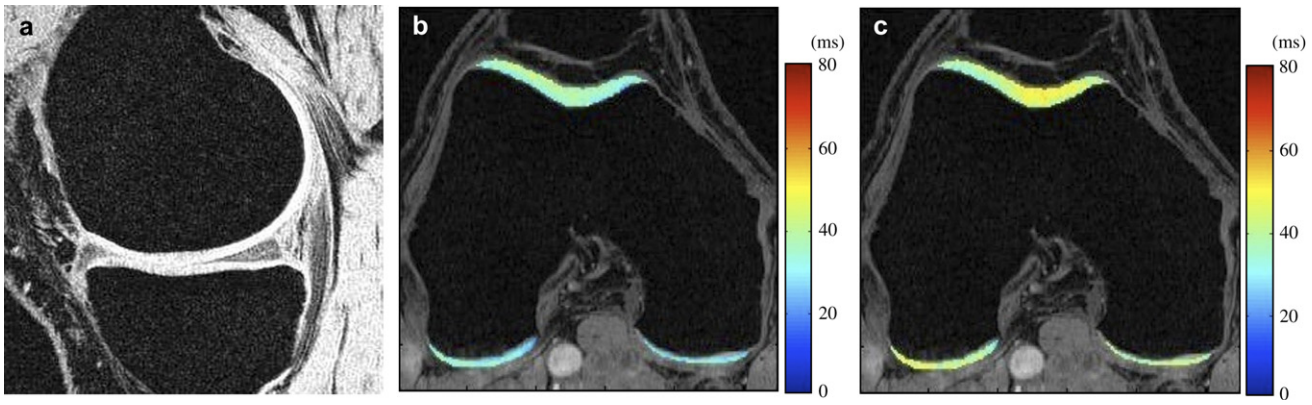

Fig. 1. T_1-weighted water excitation SPGR image (a), $T_{1\rho}$ map (b) and T_2 map (c) for a healthy control (male, 30). No radiographs were obtained, as the subject is a healthy asymptomatic control. No cartilage thinning, osteophytes and other OA symptoms were seen in MR images. The average $T_{1\rho}$ value was 40.1 ± 11.4 ms and the average T_2 value was 33.3 ± 10.5 ms in cartilage.

lesions at the lateral compartments, and two had the same lesion grade at both compartments.

There were no significant difference in the total volume and average thickness of cartilage in OA patients and control subjects (1.53 ± 0.42 cm^3/cm vs 1.27 ± 0.29 cm^3/cm for volume normalized by epicondyle length, and 1.78 ± 0.31 mm vs 1.65 ± 0.32 mm for thickness) ($P = 0.13$ and $P = 0.37$, respectively). Table III presents the mean and SD of cartilage volumes and thickness in each compartment for control subjects and OA patients. There were no significant differences in either cartilage volume or thickness for any compartment between these two groups.

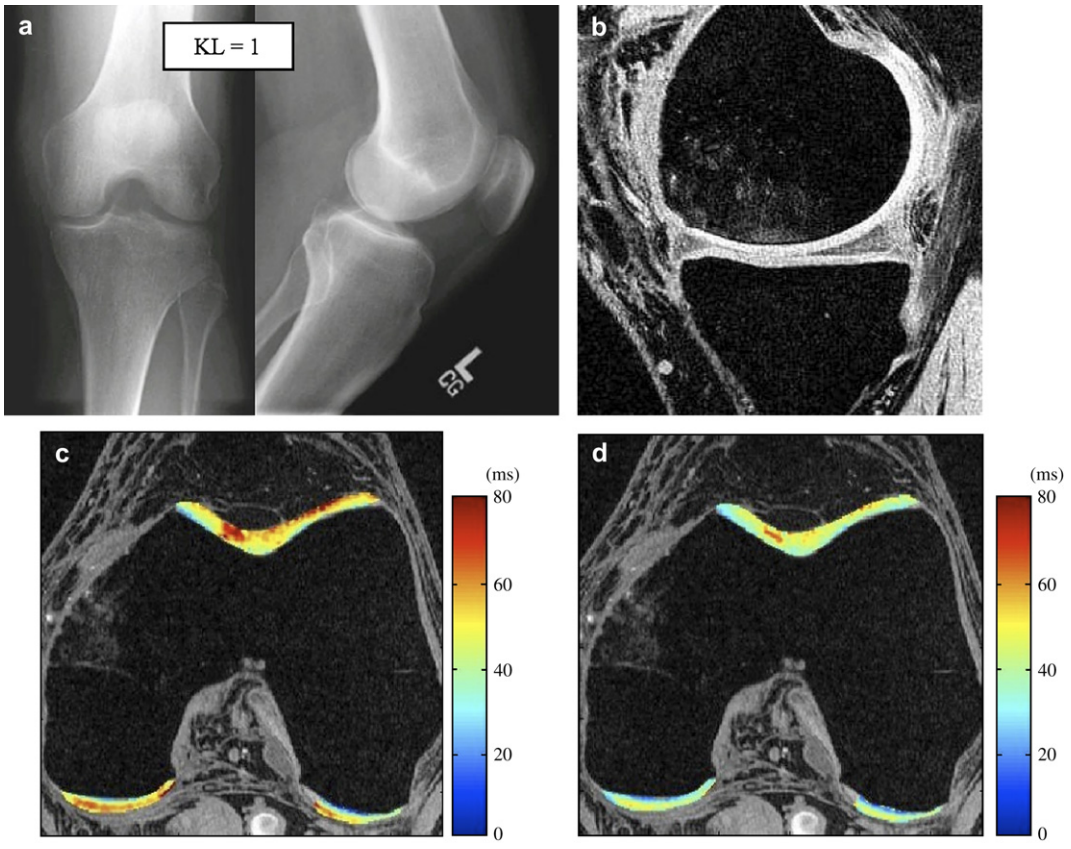

Fig. 2. Radiographs (a), T_1-weighted water excitation SPGR image (b), $T_{1\rho}$ map (c) and T_2 map (d) for a patient with mild OA (male, 66). From radiographs, no significant joint space narrowing was seen, but minimal osteophytes were observed in femoro-tibial joint and minimal to mild osteophytes were observed in femoro-patellar joint, resulting in a KL score of 1. From MR images, minimal osteophytes were also seen in femoro-tibial and femoro-patellar joints. The cartilage in medial femur and femoro-patellar compartment had grade 1 thinning. The average $T_{1\rho}$ value was 45.5 ± 14.5 ms and the average T_2 value was 35.0 ± 10.9 ms in cartilage.

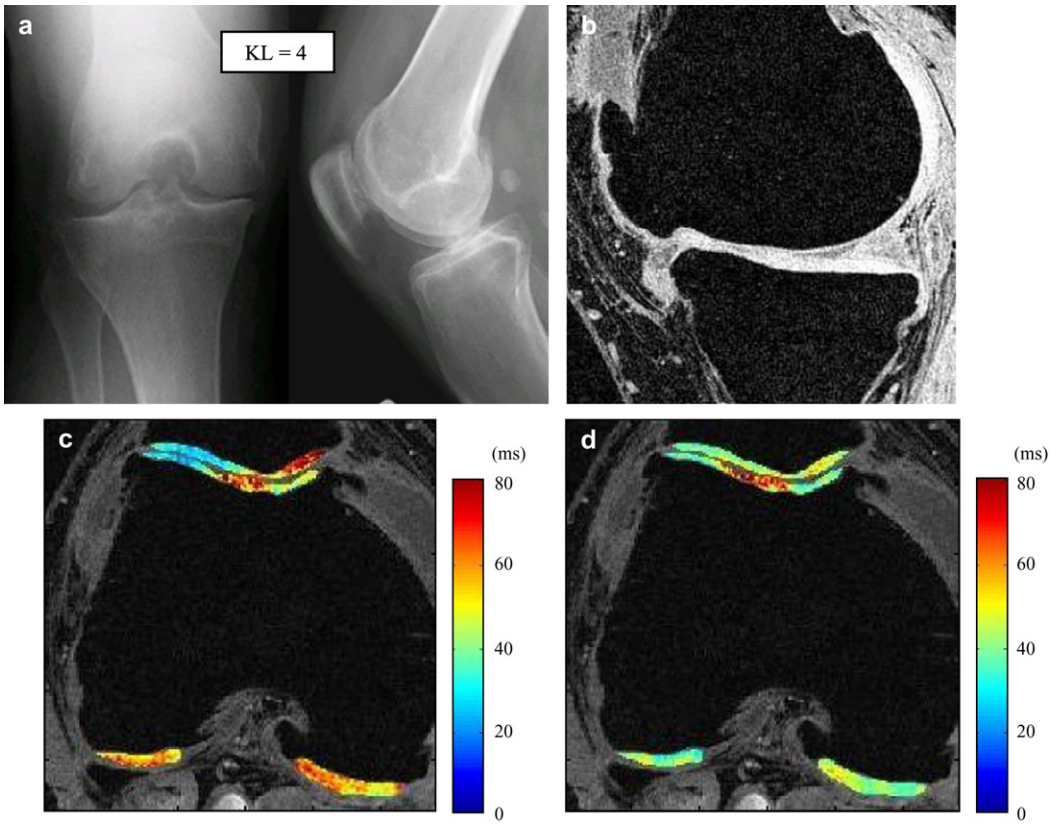

Fig. 3. Radiographs (a), T_1-weighted water excitation SPGR image (b), $T_{1\rho}$ map (c) and T_2 map (d) for a patient with advanced OA (male, 46). Based on radiographs, the patient had joint space narrowing with 1 mm in medial compartment and 3 mm in lateral compartment, and significant osteophytes in both femoro-tibial and femoro-patellar joints, resulting in a KL score of 4. In MR images, significant osteophytes were seen in both femoro-tibial and femoro-patellar joints. The cartilage had a grade 3 thinning in medial femur, medial tibia and femoro-patellar compartments, and grade 2 thinning in lateral femur and LT compartments. The average $T_{1\rho}$ value was 55.4 ± 26.0 ms and the average T_2 value was 43.8 ± 11.1 ms in cartilage.

RELATIONSHIP BETWEEN RADIOLOGICAL FINDINGS AND $T_{1\rho}$ AND T_2 QUANTIFICATION

The average $T_{1\rho}$ value increased as KL score increased based on radiographs, with 45.5 ± 3.3 ms, 47.6 ± 3.0 ms, 51.8 ± 0.7 ms, 52.4 ± 0.2 ms and 55.6 ± 0.4 ms for KL = 0 (healthy controls), 1, 2, 3, and 4, respectively [Table IV(a)].

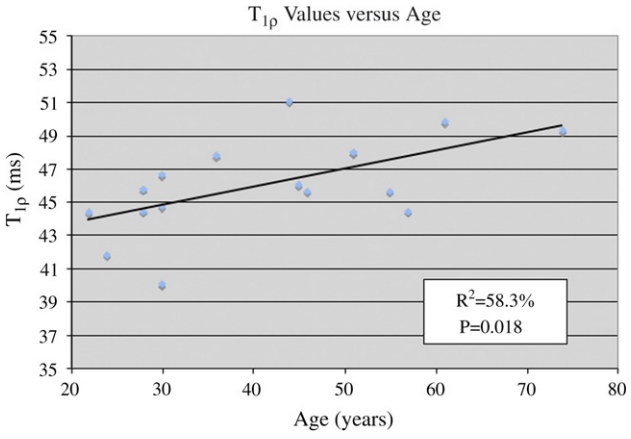

Fig. 4. Distribution of $T_{1\rho}$ values vs age in healthy volunteers. The correlation is moderate but significant with $R^2 = 58.3\%$ and $P = 0.018$.

The same trend was found between average T_2 values and KL scores, with T_2 values of 34.7 ± 2.5 ms for grade 0, 35.9 ± 1.4 ms for grade 1, 39.8 ± 2.4 ms for grade 2, 39.6 ± 0.3 ms for grade 3 and 43.0 ± 1.0 ms for grade 4, as shown in Table IV(a).

The average $T_{1\rho}$ and T_2 values increased as the overall cartilage lesion grades increased from 0 to 3 [from 46.1 ± 3.6 ms to 54.4 ± 1.5 ms for $T_{1\rho}$, and from 35.0 ± 2.5 ms to 41.4 ± 2.0 ms for T_2 as presented in Table IV(b)]. No significant correlation was found between $T_{1\rho}$ and T_2 values and cartilage volumes and thickness ($P > 0.05$).

Based on the cartilage lesion grading, we regrouped the 50 compartments for the 10 OA patients into two groups: mild OA with grades 0 and 1, and advanced OA with grades 2 and 3. The average $T_{1\rho}$ values were significantly increased in compartments with advanced OA compared with the ones with mild OA (54.3 ± 6.1 ms vs 48.4 ± 5.6 ms, $P = 0.0012$). The increase in percentage was 12.2%. The T_2 values were also elevated in the compartments with advanced OA (41.0 ± 4.5 ms vs 38.0 ± 4.8 ms, $P = 0.030$), but with an increased percentage of only 7.9%.

Discussion

In this study, we have demonstrated that both $T_{1\rho}$ and T_2 cartilage values were significantly increased in patients with OA when compared with healthy controls. $T_{1\rho}$ and T_2 values

Table IIa
Cartilage thickness (in mm, mean ± SD) in each compartment

	P	MFC	LFC	MT	LT
Controls	2.17 ± 0.62	1.51 ± 0.35	1.51 ± 0.38	1.23 ± 0.49	1.88 ± 0.28
OA patients	2.04 ± 0.53	1.65 ± 0.20	1.86 ± 0.40	1.51 ± 0.26	1.94 ± 0.49

Table IIb
Cartilage volume (normalized by epicondylar length, in cm^3/cm, mean ± SD) in each compartment

	P	MFC	LFC	MT	LT
Controls	0.23 ± 0.07	0.27 ± 0.05	0.43 ± 0.14	0.15 ± 0.04	0.19 ± 0.04
OA patients	0.33 ± 0.15	0.33 ± 0.13	0.49 ± 0.21	0.18 ± 0.05	0.21 ± 0.09

also increased with more severe radiographic OA and MR grades of cartilage degeneration.

Increased T_2 values were reported previously in degenerated cartilage in both animal models and in human subjects[7,10,32]. The values obtained in our study are consistent with the reported values, with a range from 31.3 ms to 38.7 ms for healthy controls and from 35.0 ms to 43.8 ms for patients with OA. In an effort to correlate the T_2 relaxation times with biochemical changes in cartilage, previous *in vitro* studies have reported that T_2 correlated poorly with PG content[33,34], and PG cleavage did not affect T_2 values significantly[35]. Instead, T_2 can be affected mainly by collagen content and orientation and/or water content[11,36]. It has been observed that loss of PG is an initiating event in early OA, while neither the content nor the type of collagen is altered in early OA[5]. Therefore lack of specificity to quantify PG loss may make T_2 less appealing for early detection of cartilage degeneration. In addition, the angular dependency of T_2 values with respect to the external magnetic field B_0 have made it difficult to define a 'normal' appearance of T_2 maps. As a result, it is difficult to apply T_2 values to quantify cartilage degeneration longitudinally, and the clinical results obtained with T_2 quantification remain inconclusive. This angular dependency, however, as shown in an *in vitro* study using high field (8.6 T) microscopic MRI (μMRI), can provide specific information about the collagen ultra-structure[37].

$T_{1\rho}$ has been recently proposed as an attractive alternative to evaluate biochemical changes in cartilage matrix noninvasively. $T_{1\rho}$ relaxation rate ($1/T_{1\rho}$) has been shown to decrease linearly with decreasing PG content in *ex vivo* bovine patellae[11] and has been proposed as a more specific indicator of PG content than T_2 relaxation in trypsinized cartilage[33] and in human cartilage specimens obtained from patients with severe OA who underwent total knee replacement[38]. Makela *et al.*[14] and Duvvuri *et al.*[39] have suggested that proton exchange between chemically shifted NH and OH groups of PG and the tissue water could be an important relaxation mechanism contributing to $T_{1\rho}$ relaxation. Therefore $T_{1\rho}$ may be specific to changes of PG in cartilage matrix during early stages of OA. Furthermore, $T_{1\rho}$ relaxation times do not seem to be affected by the orientation of collagen that can affect T_2 relaxation techniques[40]. Preliminary *in vivo* studies have also shown increased cartilage $T_{1\rho}$ values for patients with OA vs healthy controls[17–19]. Our results also suggested that the mean $T_{1\rho}$ values exhibit similar changes with age as seen in previous studies on T_2 relaxation times[7,41].

The results of our comparison study demonstrated that both $T_{1\rho}$ and T_2 techniques can be sensitive to cartilage degeneration. However, there is a larger range and effect size for $T_{1\rho}$ vs T_2 values, which may indicate a more sensitive method of detecting cartilage degeneration. Furthermore, although there is a significant correlation between the average $T_{1\rho}$ and T_2 values, the spatial distribution of the elevation of these two parameters can be different in OA patients, as clearly seen in Fig. 3. We will investigate the spatial correlation between $T_{1\rho}$ and T_2 values in future studies. We believe that since $T_{1\rho}$ and T_2 represent two relaxation mechanisms in tissues, they may provide complementary information on cartilage degeneration. Combining this information may enhance our ability to detect early cartilage degeneration, as well as to distinguish between different stages of degeneration.

In this study, $T_{1\rho}$ and T_2 increased with KL scores based on radiographs and overall cartilage lesion grade based on analysis of clinical MR sequences. However, due to the small sample size, we could not test the statistical significance of this correlation. In a previous study correlating *in vivo* T_2 values and OA disease severity as defined by KL scores, Dunn *et al.*[10] showed that the T_2 values were elevated significantly in mild OA (KL = 1, 2, $n = 20$) compared with healthy controls. Although there was an increasing trend of T_2 values from mild OA to severe OA (KL = 3, 4, $n = 28$), this difference was not significant. The authors proposed that with the limitations of KL grading system, in particular the emphasis on the presence of osteophytes, significant changes in T_2 values for cartilage with different KL scores are not necessarily expected. Interestingly in this study, significant differences were observed in both $T_{1\rho}$ and T_2 values between mild OA compartments (with cartilage thinning grades 0 and 1) and advanced OA compartments (with cartilage thinning grades 2 and 3) after

Table III
$T_{1\rho}$ and T_2 values (in ms, mean ± SD) in healthy controls and osteoarthritic subjects

	Controls	OA	*P* value	Effect size
$T_{1\rho}$	45.53 ± 3.28	52.04 ± 2.97	0.0002	3.7
T_2	34.74 ± 2.48	39.63 ± 2.69	0.001	3.0

Table IVa
$T_{1\rho}$ and T_2 values (in ms, mean ± SD) in subjects vs KL scores evaluated on plain radiographs

KL score	0 ($n = 10$)	I ($n = 2$)	II ($n = 3$)	III ($n = 3$)	IV ($n = 2$)
$T_{1\rho}$	45.5 ± 3.3	47.6 ± 3.0	51.8 ± 0.7	52.9 ± 0.9	55.6 ± 0.4
T_2	34.7 ± 2.5	35.9 ± 1.4	39.8 ± 2.4	40.0 ± 0.2	43.0 ± 1.0

Table IVb
$T_{1\rho}$ and T_2 values (in ms, mean ± SD) in subjects vs cartilage thinning grades evaluated on MR images

Cartilage thinning grading	0 ($n=11$)	I ($n=3$)	II ($n=2$)	III ($n=4$)
$T_{1\rho}$	46.1 ± 3.6	48.9 ± 3.0	52.4 ± 0.2	54.4 ± 1.5
T_2	35.0 ± 2.5	37.7 ± 3.1	40.3 ± 1.3	41.4 ± 2.0

we regrouped all the 50 compartments according to cartilage lesion grade.

Furthermore, among the patients with cartilage thinning observed in MR images (grade ≥ 1), six had 'spared' compartments with cartilage thinning grade 0 on the clinical MR images. The average $T_{1\rho}$ and T_2 values for these 'spared' compartments were 50.8 ± 5.4 ms and 39.4 ± 3.8 ms, respectively. These values were significantly higher than those found in the cartilage of healthy controls ($P=0.029$ and $P=0.004$ for $T_{1\rho}$ and T_2, respectively). These results suggest that cartilage degeneration, or the biochemical change, can take place in these compartments even if no morphologic changes are yet visualized.

In this study, we did not find a significant difference in cartilage volume or thickness between the healthy control and OA groups. We attribute the lack of volumetric differences to the fact that early osteoarthritic patients with less structural cartilage wear were examined and to the varying severity of OA in the disease group. The cartilage volume and thickness were slightly higher in the osteoarthritic subjects. This may be due to the increase of water content and consequently swelling of the cartilage in the early stages of OA. One example of segmented cartilage in medial compartments in a control (male, 30 years) vs an OA patient (male, 66 years) is shown in Fig. 5. Our findings also indicate that physical measures such as cartilage thickness and volume may lag behind biochemical and molecular changes which can be measured quantitatively with $T_{1\rho}$ and T_2 values.

$T_{1\rho}$ and T_2 imaging are one of the techniques that have shown the potential of MR imaging to reflect changes in the biochemical composition of cartilage with early OA. Other techniques, including sodium 23 (^{23}Na) MRI[42,43] and delayed gadolinium enhanced MRI of cartilage (dGEMRIC)[44–46] have also shown promising results in imaging cartilage biochemistry. All these techniques are complementary to standardized cartilage sensitive images and may provide information about cartilage changes (either PG or collagen) that may exist prior to structural changes in cartilage thickness or surface morphology. However, some of the techniques may have requirements that can limit their clinical use. The dGEMRIC technique, which has been validated in multiple studies to allow assessment of the PG component of articular cartilage, requires a several hour wait after either an intravenous or intraarticular injection of the contrast agent (Gadopentetic acid) for effective penetration. ^{23}Na MR imaging, which uses sodium concentrations as a marker for PG loss, is of limited clinical use because of the inherent low sensitivity of sodium signal and the limited availability of sodium MRI (requires special coils and hardware).

$T_{1\rho}$ and T_2 mapping does not require the use of special hardware, coils or contrast. Our study was implemented on a 3 T MR scanner because of the advantages afforded by using a higher field strength (such as increased signal to noise ratio and higher resolution), but $T_{1\rho}$-weighted MR images can be easily obtained on more readily available 1.5 T scanners[47].

A potential limitation of this study was that average $T_{1\rho}$ and T_2 values were quantified within the entire cartilage surface or in a specific compartment of the knee. Mosher and coworkers have developed techniques examining the spatial variation of T_2 within cartilage and reported changes in different layers with age and with cartilage degeneration[48]. It may be helpful to further investigate the spatial variation of $T_{1\rho}$ in different layers and compare it with that of T_2 values in both healthy controls and osteoarthritic subjects to better localize areas of cartilage degeneration.

In conclusion, *in vivo* $T_{1\rho}$ and T_2 mapping techniques have demonstrated feasibility in detecting cartilage degeneration. Quantitative cartilage imaging may enhance our ability to detect subtle, early matrix changes associated with cartilage injuries when used in conjunction with standardized cartilage sensitive imaging. We are currently investigating the ability of quantitative imaging to detect cartilage injuries associated with ligament tears[49]. Development of noninvasive

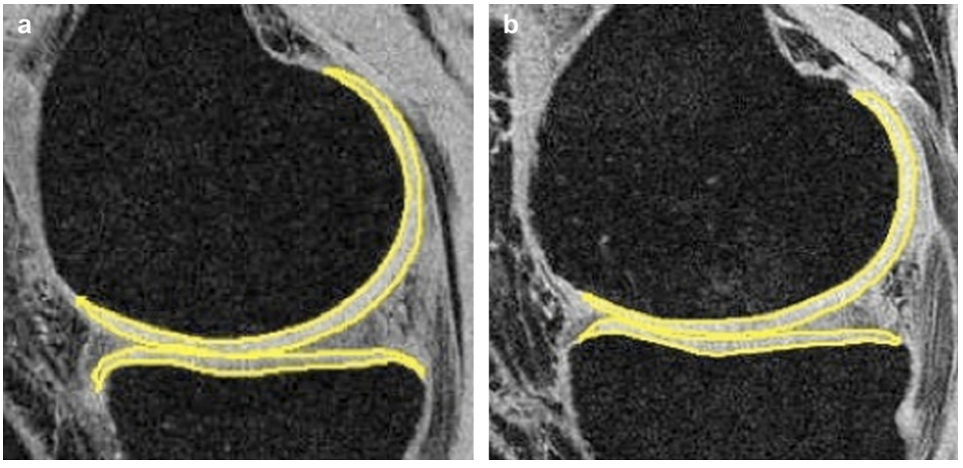

Fig. 5. Segmented femoral and tibial cartilage in medial compartments of a healthy control (a, male, 30) and an OA patient (b, male, 66). The average thickness (in mm) is 1.68 vs 1.84 (control vs OA) in MFC, and 1.63 vs 1.71 (control vs OA) in MT. The volume (normalized by epicondylar length, in cm^3/cm) is 0.31 vs 0.35 (control vs OA) in MFC, and 0.20 vs 0.19 (control vs OA) in MT. The slightly increased cartilage volume and thickness may due to the increase of water content and consequently swelling of the cartilage in the early stages of OA.

methods to assess early cartilage matrix changes is potentially important to initiate early treatment, monitor disease progression and to follow-up operative cartilage repair and resurfacing.

Acknowledgments

The authors would like to thank Dr Robert Stahl for his help with the radiograph data. The research was supported by NIH RO1 AG17762, RO1 AR46905 and K25 AR053633.

References

1. Brandt KD, Doherty M, Lohmander LS, Eds. Osteoarthritis. New York: Oxford University Press Inc 1998.
2. Rogers J, Watt I, Dieppe P. A comparison of the visual and radiographic detection of bony changes at the knee joint. BMJ 1990;300:367–8.
3. Chan WP, Lang P, Stevens MP, Sack K, Majumdar S, Stoller DW, *et al*. Osteoarthritis of the knee: comparison of radiography, CT, and MR imaging to assess extent and severity. AJR Am J Roentgenol 1991;157(4): 799–806.
4. Gray ML, Eckstein F, Peterfy C, Dahlberg L, Kim YJ, Sorensen AG. Toward imaging biomarkers for osteoarthritis. Clin Orthop 2004;(Suppl 427):S175–81.
5. Dijkgraaf LC, de Bont LG, Boering G, Liem RS. The structure, biochemistry, and metabolism of osteoarthritic cartilage: a review of the literature. J Oral Maxillofac Surg 1995;53(10):1182–92.
6. Xia Y, Farquhar T, Burton-Wuster N, Ray E, Jelinski L. Diffusion and relaxation mapping of cartilage-bone plugs and excised disks using microscopic magnetic resonance imaging. Magn Reson Med 1994;31:273–82.
7. Mosher TJ, Dardzinski BJ, Smith MB. Human articular cartilage: influence of aging and early symptomatic degeneration on the spatial variation of T2—preliminary findings at 3 T. Radiology 2000;214(1):259–66.
8. Dardzinski BJ, Laor T, Schmithorst VJ, Klosterman L, Graham TB. Mapping T2 relaxation time in the pediatric knee: feasibility with a clinical 1.5-T MR imaging system. Radiology 2002;225(1):233–9.
9. David-Vaudey E, Ghosh S, Ries M, Majumdar S. T2 relaxation time measurements in osteoarthritis. Magn Reson Imaging 2004;22(5):673–82.
10. Dunn TC, Lu Y, Jin H, Ries MD, Majumdar S. T2 relaxation time of cartilage at MR imaging: comparison with severity of knee osteoarthritis. Radiology 2004;232(2): 592–8.
11. Duvvuri U, Reddy R, Patel SD, Kaufman JH, Kneeland JB, Leigh JS. T1rho-relaxation in articular cartilage: effects of enzymatic degradation. Magn Reson Med 1997;38(6):863–7.
12. Nugent AC, Johnson GA. T1rho imaging using magnetization-prepared projection encoding (MaPPE). Magn Reson Med 2000;43(3):421–8.
13. Akella SV, Regatte RR, Gougoutas AJ, Borthakur A, Shapiro EM, Kneeland JB, *et al*. Proteoglycan-induced changes in T1rho-relaxation of articular cartilage at 4T. Magn Reson Med 2001;46(3):419–23.
14. Makela HI, Grohn OH, Kettunen MI, Kauppinen RA. Proton exchange as a relaxation mechanism for T1 in the rotating frame in native and immobilized protein solutions. Biochem Biophys Res Commun 2001; 289(4):813–8.
15. Mlynarik V, Szomolanyi P, Toffanin R, Vittur F, Trattnig S. Transverse relaxation mechanisms in articular cartilage. J Magn Reson 2004;169(2):300–7.
16. Redfield AG. Nuclear spin thermodynamics in the rotating frame. Science 1969;164:1015–23.
17. Duvvuri U, Charagundla SR, Kudchodkar SB, Kaufman JH, Kneeland JB, Rizi R, *et al*. Human knee: *in vivo* T1(rho)-weighted MR imaging at 1.5 T—preliminary experience. Radiology 2001;220(3):822–6.
18. Regatte RR, Akella SV, Wheaton AJ, Lech G, Borthakur A, Kneeland JB, *et al*. 3D-T1rho-relaxation mapping of articular cartilage: *in vivo* assessment of early degenerative changes in symptomatic osteoarthritic subjects. Acad Radiol 2004;11(7):741–9.
19. Li X, Han E, Ma C, Link T, Newitt D, Majumdar S. *In vivo* 3T spiral imaging based multi-slice T(1rho) mapping of knee cartilage in osteoarthritis. Magn Reson Med 2005;54(4):929–36.
20. Hangody L, Fules P. Autologous osteochondral mosaicplasty for the treatment of full-thickness defects of weight-bearing joints: ten years of experimental and clinical experience. J Bone Joint Surg Am 2003; 85-A(Suppl 2):25–32.
21. Steadman J, Briggs K, Rodrigo J, Kocher M, Gill T, Rodkey W. Outcomes of microfracture for traumatic chondral defects of the knee: average 11-year follow-up. Arthroscopy 2003;19(5):477–84.
22. Knutsen G, Engebretsen L, Ludvigsen T, Drogset J, Grontvedt T, Solheim E, *et al*. Autologous chondrocyte implantation compared with microfracture in the knee. A randomized trial. J Bone Joint Surg Am 2004;86-A: 455–64.
23. Brandt K, Mazzuca S, Katz B, Lane K, Buckwalter K, Yocum D, *et al*. Effects of doxycycline on progression of osteoarthritis: results of a randomized, placebo-controlled, double-blind trial. Arthritis Rheum 2005;52(7): 2015–25.
24. Brittain JH, Hu BS, Wright GA, Meyer CH, Macovski A, Nishimura DG. Coronary angiography with magnetization-prepared T2 contrast. Magn Reson Med 1995; 33(5):689–96.
25. Oh J, Cha S, Aiken AH, Han ET, Crane JC, Stainsby JA, *et al*. Quantitative apparent diffusion coefficients and T2 relaxation times in characterizing contrast enhancing brain tumors and regions of peritumoral edema. J Magn Reson Imaging 2005 Jun;21(6): 701–8.
26. Kellgren J, Lawrence J. Radiologic assessment of osteoarthritis. Ann Rheum Dis 1957;16:494–502.
27. Hart D, Spector T. Assessment of changes in joint tissues in patients treated with a disease-modifying osteoarthritis drug (DMOAD): monitoring outcomes, Osteoarthritis. Oxford, England: Oxford University Press 1998. pp. 450–8.
28. Link TM, Steinbach LS, Ghosh S, Ries M, Lu Y, Lane N, *et al*. Osteoarthritis: MR imaging findings in different stages of disease and correlation with clinical findings. Radiology 2003;226(2):373–81.
29. Carballido-Gamio J, Bauer JS, Lee KY, Krause S, Majumdar S. Combined image processing techniques for characterization of MRI cartilage of the knee. 27th Annual Conference IEEE Engineering in Medicine and Biology Society (EMBS) 2005 Sep 1–4; Shanghai, China.
30. Blumenkrantz G, Lindsey CT, Dunn TC, Jin H, Ries MD, Link TM, *et al*. A pilot, two-year longitudinal study of the interrelationship between trabecular bone

and articular cartilage in the osteoarthritic knee. Osteoarthritis Cartilage 2004;12(12):997–1005.
31. Rueckert D, Sonoda LI, Hayes C, Hill DL, Leach MO, Hawkes DJ. Nonrigid registration using free-form deformations: application to breast MR images. IEEE Trans Med Imaging 1999;18(8):712–21.
32. Mosher T, Dardzinski B. Cartilage MRI T2 relaxation time mapping: overview and applications. Semin Musculoskelet Radiol 2004;8(4):355–68.
33. Regatte RR, Akella SV, Borthakur A, Kneeland JB, Reddy R. Proteoglycan depletion-induced changes in transverse relaxation maps of cartilage: comparison of T2 and T1rho. Acad Radiol 2002;9(12):1388–94.
34. Toffanin R, Mlynarik V, Russo S, Szomolanyi P, Piras A, Vittur F. Proteoglycan depletion and magnetic resonance parameters of articular cartilage. Arch Biochem Biophys 2001;390(2):235–42.
35. Nieminen MT, Toyras J, Rieppo J, Hakumaki JM, Silvennoinen J, Helminen HJ, *et al*. Quantitative MR microscopy of enzymatically degraded articular cartilage. Magn Reson Med 2000;43(5):676–81.
36. Gray M, Burstein D, Xia Y. Biochemical (and functional) imaging of articular cartilage. Semin Musculoskelet Radiol 2001;5(4):329–43.
37. Xia Y. Relaxation anisotropy in cartilage by NMR microscopy (muMRI) at 14-micron resolution. Magn Reson Med 1998;39(6):941–9.
38. Regatte R, Akella S, Lonner J, Kneeland J, Reddy R. T1rho relaxation mapping in human osteoarthritis (OA) cartilage: comparison of T1rho with T2. J Magn Reson Imaging 2006;23(4):547–53.
39. Duvvuri U, Goldberg AD, Kranz JK, Hoang L, Reddy R, Wehrli FW, *et al*. Water magnetic relaxation dispersion in biological systems: the contribution of proton exchange and implications for the noninvasive detection of cartilage degradation. Proc Natl Acad Sci U S A 2001;98(22):12479–84.
40. Akella SV, Regatte RR, Wheaton AJ, Borthakur A, Reddy R. Reduction of residual dipolar interaction in cartilage by spin-lock technique. Magn Reson Med 2004;52(5):1103–9.
41. Mosher T, Liu Y, Yang Q, Yao J, Smith R, Dardzinski B, *et al*. Age dependency of cartilage magnetic resonance imaging T2 relaxation times in asymptomatic women. Arthritis Rheum 2004;50(9):2820–8.
42. Reddy R, Insko EK, Noyszewski EA, Dandora R, Kneeland JB, Leigh JS. Sodium MRI of human articular cartilage *in vivo*. Magn Reson Med 1998;39(5):697–701.
43. Shapiro EM, Borthakur A, Gougoutas A, Reddy R. 23Na MRI accurately measures fixed charge density in articular cartilage. Magn Reson Med 2002;47(2):284–91.
44. Bashir A, Gray ML, Burstein D. Gd-DTPA2– as a measure of cartilage degradation. Magn Reson Med 1996;36(5):665–73.
45. Bashir A, Gray ML, Hartke J, Burstein D. Nondestructive imaging of human cartilage glycosaminoglycan concentration by MRI. Magn Reson Med 1999;41(5):857–65.
46. Nieminen MT, Rieppo J, Silvennoinen J, Toyras J, Hakumaki JM, Hyttinen MM, *et al*. Spatial assessment of articular cartilage proteoglycans with Gd-DTPA-enhanced T1 imaging. Magn Reson Med 2002;48(4):640–8.
47. Borthakur A, Wheaton A, Charagundla SR, Shapiro EM, Regatte RR, Akella SV, *et al*. Three-dimensional T1rho-weighted MRI at 1.5 Tesla. J Magn Reson Imaging 2003;17(6):730–6.
48. Smith HE, Mosher TJ, Dardzinski BJ, Collins BG, Collins CM, Yang QX, *et al*. Spatial variation in cartilage T2 of the knee. J Magn Reson Imaging 2001;14(1):50–5.
49. Lozano J, Li X, Link T, Safran M, Majumdar S, Ma C. Detection of posttraumatic cartilage injury using quantitative T1rho magnetic resonance imaging. A report of two cases with arthroscopic findings. J Bone Joint Surg Am 2006;88(6):1349–52.